SYNTHESIS OF CERTAIN ALPHA, OMEGA–AMINOALCOHOLS FROM CYCLIC AMINES

By

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TABLE OF CONTENTS

	Page
Review of Literature and Introduction	1
Discussion of Methods and Experimental Procedures	6
The Direct Alkylation Method	8
First Attempt to Prepare 10-Morpholinodecanol-1 by Alkylation	9
Second Attempt to Prepare 10-Morpholinodecanol-1 by Alkylation	11
Theoretical Considerations	12
The Chlorohydrin Method	18
Sample Procedures	
(a) Preparation of 8-Morpholinooctanol-1	20
(b) Preparation of N-Phenyl-N'-(5-Hydroxypentyl) Piperazine	21
Purification of Compounds	22
Preparation of Derivatives	22
Characterization of Compounds	22
Sample Derivative Preparation	
Preparation of N-Phenyl-N'-(10-Hydroxydecyl) Piperazine	23
Preparation of Intermediates	24
Table I	
Physical Data on Morpholinoalcohols	27

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Figure I

Boiling Point Curves of Morpholinoalcohols and Dimorpholinoalkanes 28

Table II

Analytical Data on Morpholinoalcohols 29

Table III

Aryl Urethanes of Morpholinoalcohols 30

Table IV

Morpholinoalcohols by Alkylation 31

Table V

Physical Data on α,ω-Dimorpholinoalkanes 32

Table VI

Analytical Data on α,ω-Dimorpholinoalkanes 33

Table VII

Physical and Analytical Data on N-Phenyl-N'-(ω-Hydroxyalkyl) Piperazines 34

Table VIII

Phenyl Urethanes of N-Phenyl-N'-(ω-Hydroxyalkyl) Piperazines 35

Figure III

Melting Point Curves of the N-Phenyl-N'-(ω-Hydroxyalkyl) Piperazines and Their Phenyl Urethanes 36

Table IX

Boiling Points of the Di-(n-butyl) Esters of Dicarboxylic Acids 37

Table X

Boiling Points and Melting Points of α,ω-Glycols as Determined in This Investigation 38

Table XI

Physical Data on α,ω-Chlorohydrins, This Investigation 39

Figure II

Boiling Point Curve of α,ω-Chlorohydrins 40

Table XII

Physical Data on α,ω-Chlorohydrins Reported in the Literature 41

Table XIII

Melting Points of Aryl Urethanes of α,ω-Chlorohydrins, This Investigation and Literature 42

Summary 43

Bibliography 45

Acknowledgments 48

Biography 49

Committee Report 50

Review of Literature and Introduction

This investigation was initiated with two primary objectives:

1. Improvement in the methods of preparation of alpha, omega-aminoalcohols.

2. A continuation of the research of the organic laboratories of the University of Florida upon various cyclic amines.

Alpha, omega-aminoalcohols are those in which the amine group is on one end of a carbon chain and the alcohol group on the other. They may be represented by the general formula,

where R and R' are hydrogen atoms or alkyl groups, and n is an integer. The term 'alpha, omega-aminoalcohol' might possibly include compounds in which the carbon chain is branched, but the author has found no example of this. In this dissertation, the term is used for straight carbon chains only. The research was limited to compounds where n was four through ten.

A review of the literature has shown that a number of ethanol and propanol amines have been made and studied. These have generally been made from reaction of the appropriate amine with ethylene or trimethylene chlorohydrin, or with the corresponding oxides. The work has undoubtedly been stimulated by the availability of these reagents. The interest in preparing analogs of novocaine, which is an

ester of beta-diethylaminoethanol, has also been a factor.

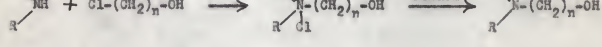
Higher members of the alpha, omega series, beginning with the delta-butanolamines are rarer. Von Braun[5] was among the first to report syntheses of alpha, omega-aminoalcohols. He reacted a secondary amine with an omega-bromoalkylester and hydrolyzed the ester:

$$2R_2NH + Br(CH_2)_nOCOC_6H_5 \longrightarrow R_2N(CH_2)_nOCOC_6H_5 + R_2NH.HBr$$

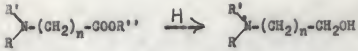
$$R_2N(CH_2)_nOCOC_6H_5 + H_2O \longrightarrow R_2N(CH_2)_nOH + C_6H_5COOH$$

Magidson and Strukov[4], in their preparation of 8-aminoquinoline derivatives for study as antimalarials, prepared 4-diethylaminobutanol and 5-diethylaminopentanol by malonic ester syntheses from diethylaminoethyl chloride and diethylaminopropyl chloride.

One of the most direct syntheses of alpha, omega-aminoalcohols was reported in a British patent granted to Pyman and Levene.[6] A secondary amine was reacted with a chlorohydrin:



The patent also includes the reduction of omega-amino carboxylic acid esters with sodium and alcohol.



For the compounds claimed in the patent, the amino group was a dialkyl or piperidyl residue, and n was seven through eleven.

Adkins and co-workers have reported syntheses of amino-alcohols by catalytic methods in recent years. Adkins, Kuick, Farlow, and Wojcik[7,20] prepared 5-piperidinopentanol-1 and 4-piperidinobutanol-1 by catalytic hydrogenation of ethyl gamma-piperidinobutyrate and ethyl delta-piperidinovalerate. Paden and Adkins[8,21] reported 5-piperidino-pentanol-1 by catalytic hydrogenation of di-N-pentamethylene gluter-amide, and 4-phenethylamino-butanol-1 from the catalyzed reaction of phenethylamine and butanediol-1,4. Sauer and Adkins[9] obtained good yields of 4-piperidinobutanol-1 and 6-piperidinohexanol-1 by catalytic hydrogenation of alpha, omega-amidoesters.

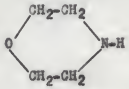
In the work reported here, the synthesis of alpha, omega-aminoalcohols of four through ten carbon atoms was accomplished in two ways:

1. By reaction of an amine with alpha, omega-chlorohydrins[6].

2. By reaction of an amine with alpha, omega-glycols in the presence of copper chromium oxide catalyst, using the method of Adkins and co-workers[8,10].

Two secondary amines, morpholine and N-phenylpiperazine were used.

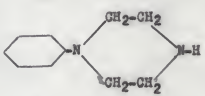
Morpholine has the structure:



It was discovered by Knorr in 1889, but was not commercially available until 1935[12]. Morpholine is an excellent solvent; compared with common solvents, its solvent power is greater than dioxane which is greater than pyridine which is greater than benzene. The many references in recent literature to morpholine indicate a wide-spread interest in it.

The only morpholinealcohols which appear to have been prepared previous to the present research are beta-morpholinoethanol and gamma-morpholinopropanol. Some derivatives of these[12,13] have been found to have good anesthetic qualities.

N-Phenylpiperazine was first prepared by Prelog and Driza in 1933[14]. It was independently synthesized in the Organic Chemistry Laboratories of the University of Florida by Pollard and MacDowell in 1934[15]. It has the structure:



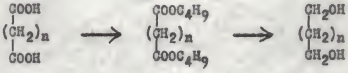
The only alcohol derivative reported is N-phenyl,N'-(beta-hydroxyethyl)-piperazine[16,17]. Its derivatives are reported to have anesthetic qualities[17].

The limited investigation of alpha,omega-aminoalcohols with a carbon chain of four or more atoms may be ascribed to two factors: First, the intermediates necessary in the preparation are not easy to obtain, Second, various workers[1,2] in the field of physiologically active compounds have concluded that lengthening the carbon chain in omega-amino derivatives decreases the desirable properties. There is limited contrary evidence[3]. Magidson and Strukov[4], in their investigations of derivatives of 8-aminoquinoline, found an alternating therapeutic effect upon increasing the length of the diethylaminoalkyl chain. It is evident that data on the subject is insufficient.

It seems reasonable that a pharmocological investigation of derivatives of the two series of alpha, omega-aminoalcohols reported in this dissertation would furnish worthwhile data. Further, the derivatives reported herein are urethans. It has been found[18,19] that urethans make good anesthetics.

Discussion of Methods and Experimental Procedures

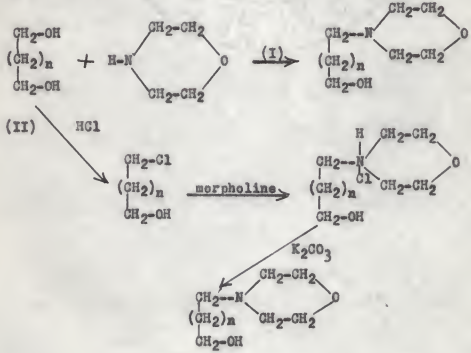
The general procedure in preparation of the alpha, omega-glycols used was to start with a dibasic acid, make the dibutyl ester and hydrogenate under high pressure at 250° with a copper-chromium oxide catalyst[26] by the method of Adkins and co-workers[22,23,24,25]:



From the glycols, the alpha, omega-morpholinealcohols were made by two methods.

(I) By direct reaction with morpholine by the method of Adkins and co-workers[27,28].

(II) By converting the glycols to chlorohydrins and reacting these with morpholine.



The N-phenyl,N'-(omega-hydroxyalkyl)-piperazines were made by the chlorohydrin method only.

These methods will be discussed separately.

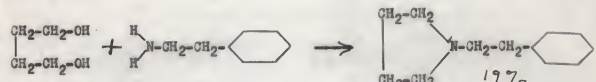
The Direct Alkylation Method

This method is based upon the discovery by Paden and Adkins[27] that amines can be alkylated by reacting them with glycols in the presence of copper-chromium oxide (and hydrogen, presumably only as an inert atmosphere). They were primarily interested in synthesizing pyrrolidines, piperidines, and hexahydroazepines from tetramethylene, pentamethylene, and hexamethylene glycols with the primary amines phenethyl, benzyl and n-amyl:

$$\begin{matrix} OH \\ | \\ (CH_2)_n \\ | \\ OH \end{matrix} + H_2N\text{-}R \longrightarrow (CH_2)_n{=}N\text{-}R$$

where n is 4,5, or 6, and R is phenethyl, benzyl, or n-amyl. By carrying out the reaction at 250°C for one hour in 600-800 cc. dioxane per mole, with 30-60 g. copper-chromium oxide per mole, and using the amine and glycol in mole-for-mole ratio, they obtained good yields of the desired cyclic amines. Under these conditions, they got no aminoalcohol.

They report, however, one experiment in which butanediol-1,4 was reacted with phenethyl amine at 200° (instead of 250°) for half an hour (instead of one hour). Their results may be indicated graphically:



The authors state "No more experiments along this line were carried out, but it is quite possible that by modifying the conditions, higher yields of aminoalcohols of this type might be obtained".(a)

Upon the evidence of this one experiment, it was decided to attempt to prepare morpholinoalcohols by catalytic alkylation. Such a synthesis has the advantage of being one step shorter than the chlorohydrin method.

The first experiment was as follows.

First Attempt to Prepare 10-Morpholinodecanol by Alkylation

Five-tenths mole (87 g.) of decamethylene glycol, 0.5 mole of morpholine (43.5 g.), 300 cc. redistilled dioxane, and 30 g. copper-chromium oxide catalyst[26] were put in the bomb, heated to 250° (without hydrogen), shaken two hours. At the end of this time, the shaking was stopped and the heat cut off. Upon cooling, the bomb was opened and the catalyst filtered off with the use of a filter aid. The dioxane was distilled off through column C(b). The boiling point was

(a) Reference 27, page 2492.

(b) Column C is 30 cm. long by 1.5 cm. diameter (inside), has a total

90-103°, indicating the presence of water.

A small amount of remaining dioxane and morpholine was removed at the water pump, and the remainder was fractionated at 2 mm.. Fractions obtained:

1. B. P. 137-147, mostly 143-144°. Weight 51.6 g. Solidified on cooling.

2. B. P. 146-161°. Weight 18.7 g. Solidified on cooling.

3. B. P. 161° for a few drops, then the temperature began falling. Distillation was cut off. Weight of fraction, 1.8 g., M. P. 35-40°. Probably 10-morpholinodecanol-1. (Pure 10-morpholinodecanol-1 as prepared by the chlorohydrin method had B. P. 163-4° (uncorr.), M. P. 39.5-40.5°. Decamethylene glycol boils at 153-4° at 3 mm..) A small amount of residue in the distillation flask also appeared to be 10-morpholinodecanol-1. Fractions 1 and 2 were apparently mostly recovered glycol.

Thus, there was only a small amount of alkylation in this experiment.

It was decided to repeat, using a longer time for alkylation. It was also decided to carry out the reaction under hydrogen pressure as did Adkins and Paden, although there seems to be no theoretical reason for hydrogen to be present.

(b) cont'd. condensation type head, is air-jacketed with a spiral heating coil. It is packed with 5 by 5 mm. Raschig rings.

Second Attempt to Prepare 10-Morpholinodecanol-1 by Alkylation

Four-tenths mole (70 g.) decamethylene glycol, 0.4 mole (34.8 g.) morpholine, 300 cc. dioxane, 40 g. copper-chromium oxide catalyst (32 g. of which had been previously used in an ester reduction) were reacted under 1,500 lbs. per square inch of hydrogen for 6 hours at 240-255°C. The products were fractionated as before at 2 mm. pressure. Fractions obtained:

	B. P.	M. P.	Weight
1.	135-143-5-160°		25.0 g.
2.	158-63		6.2
3.	163-5	34-7°	20.6
4.	165-85		14.4
5.	185-7	43-7	15.9
		Total weight	82.1 g.

This was 78% of the weight of the starting material. It is estimated that the remaining 22% is accounted for as losses in the column, residue, and losses in handling. (In subsequent preparations, a higher percentage of material was recovered.)

The yields, based on the glycol used, were:

Fraction 2, $\frac{20.6}{0.4 \times 243} = 21\%$ of pure aminoalcohol.

Fraction 5, $\frac{16}{0.4 \times 312} = 13\%$ of pure diamine.

Here, it was decided to vary the conditions on the remaining six glycols for the purpose of increasing the yield of pure aminoalcohol. Since the amine used was a secondary amine, only two products

were possible without breaking the morpholine ring, or without hydrogenolysis of the glycol. Under the conditions used, such wide reactions would be unlikely. Thus the reactions to be expected are:

1. Morpholine + Glycol ⟶ Morpholinoalcohol + Water
2. 2 x Morpholine + Glycol ⟶ Dimorpholinoalkane + 2 x Water

Comparing with the time of reaction (1/2 hour) used by Adkins and Paden[27] for a primary amine and glycol, it would seem that the six hours time of reaction used in the second 10-morpholinodecanol-1 preparation above is ample for a complete reaction, even though the quality of the catalyst used might be poor. Results show that this time is sufficient, as little unreacted morpholine was recovered in this and subsequent preparations. This constant time factor of six hours was used in all experiments.

Likewise, it would seem that increasing the proportion of catalyst used would have little effect, so this factor was kept constant also. Assuming variation in the amount of dioxane (used as a solvent and diluent for the water formed) would have little effect, then only two major factors remain to be considered - temperature and proportion of reactants used. Since only enough of each glycol was on hand for one run, it was decided to keep one of these variables constant for the series. The temperature was kept constant and the proportion of morpholine to glycol was varied.

The experimental runs were carried out essentially in the same manner as the second alkylation experiment above. Results are

summarized in TABLE IV. Best yields of pure morpholinoalcohol were obtained when a 25% excess of morpholine was used. When a mole-for-mole experiment was conducted, as in the case of hexamethylene glycol plus morpholine and the case of decamethylene glycol plus morpholine, the yields of both aminoalcohol and diamine were low; when a 50% excess of morpholine was used, as in the case of octamethylene glycol plus morpholine, the diamine was obtained in the larger yield.

Use of a 25% excess of morpholine gave higher yields of pure aminoalcohol in three cases: with tetramethylene glycol, pentamethylene glycol and nonamethylene glycol. In the fourth case, with heptamethylene glycol, the yield of pure diamine was greater.

In each case, some unreacted glycol was recovered, but no attempt was made to obtain it pure. The presence of glycol in the first fraction in each case was indicated by the boiling point range of this fraction.

To get a rough idea of the actual percentages of glycol, aminoalcohol, and diamine present after the reaction is complete, estimates of the constitution of the intermediate fractions were made for the case of nonamethylene glycol plus morpholine.

In the experiment, 11/32 mole (55 g.) of $HO-(CH_2)_9-OH$, 1 1/4 x 11/32 mole (37.4 g.) of morpholine, 250 cc. dioxane, and 11 g. copper-chromium oxide catalyst were heated six hours at 240-260°, with shaking. The products were treated as previously described, with final

fractionation through column B[a]. Fractions obtained at 5 mm. pressure:

	B. P.	Weight	Refractive Index
1.	150.0-174.5	12.7	
2.	174.5-176.5	21.7	N_D^{24} 1.4741
3.	176.5-178.5	8.3	$N_D^{23.5}$ 1.4751
(On changing receiving flasks, the temperature rose to 197.5°)			
4.	197.5-202.5	5.1	$N_D^{24.2}$ 1.4783
5.	203.0-204.0	24.0	$N_D^{24.7}$ 1.4790

Percent yields, based on glycol used: For 9-morpholinononanol-1, fraction 2 plus fraction 3 equals 38.1%; for 1,9-dimorpholinononane, fractions 4 plus 5 equals 28.4%. Assuming 10 g. of fraction 1 is glycol (the material mostly solidified), then the percent recovery of glycol is 15.2%. The remaining 2.7 g. in fraction 1 must be considered aminoalcohol, and would represent 3.4%, making the total yield of aminoalcohol 38.1% plus 3.4% equals 41.5%. Thus the total distilled material would be 41.5% plus 15.2% plus 24.8% or 85%. Assuming the unaccounted for material (about 10 g.) was the residue in the column and distilling flask, and was diamine, then the estimated diamine formed is 28.4% plus 12% or 40.4%. Roughly then, the reaction product is composed of 41.5% 9-morpholinononanol-1, 40.4% of 1,9-dimorpholinononane, and 18.2% of unreacted glycol.

(a) Column B was 29 inches long, 1 1/4 inches inside diameter, has a total condensation type head, and an air jacket heated by a nichrome spiral. It was packed with 6 x6 mm. pieces of glass tubing.

It will be noted that approximately equal molecular proportions of aminoalcohol and diamine were obtained. Similar estimations of the composition of intermediate fractions for the second 10-morpholinodecanol-1 preparation, which was discussed on p. 11, indicate that equal yields of about 30% aminoalcohol and 30% diamine were formed there. In the case of hexamethylene glycol plus morpholine, in which a mole-per-mole ratio was used, like calculation gives 40% glycol recovered, 30% 6-morpholinohexanol-1, and 30% 1,6-dimorpholinohexane; again equimolecular proportions of aminoalcohol and diamine were obtained.

In the case of octamethylene glycol, estimation from the intermediate fractions give 11% glycol recovered, 34% 8-morpholinooctanol-1, and 46% 1,8-dimorpholinooctane. In this experiment 1.5 moles of morpholine per mole of glycol was used. There was one particular feature about this reaction - the temperature was allowed to rise accidently from 240° to 307° during the last hour of reaction. Bain[(a)] has recently discovered that at 275°, cyclohexylamine can be hydrolyzed to cyclohexanol. The presence of glycol in the reaction products here could be explained by assuming such a reaction, which would be a reversal of the alkylation process. An incomplete alkylation must also be considered as a possibility.

Excluding the latter experiment, which was irregular, it is seen that approximately equal molecular proportions of amino-

(a) Unpublished work, Organic Chemistry Laboratories, University of Florida.

alcohol and diamine were obtained in all the experiments, regardless of whether one mole or one and a quarter moles of amine were used for each mole of glycol. If this were found to be true for other proportions of amine, it would indeed be interesting. At the present time, there is insufficient data to draw any conclusions as to the mechanism of the reaction. One might guess that the reactions,

$$\text{Glycol} + \text{Amine} \longrightarrow \text{Aminoalcohol} + \text{Water}$$

$$\text{Aminoalcohol} + \text{Amine} \longrightarrow \text{Diamine} + \text{Water}$$

would be consecutive second order reactions, but it is hard to see how equal amounts of aminoalcohol and diamine would be formed in every case, unless the reactions are reversible, and thus attain an equilibrium. The results of the experiment with octamethylene glycol (p. 15) indicate in themselves that the reaction might be reversible. In theorizing, one must also consider other possible types of reactions which might explain the results - for instance, the possibility of simultaneous reactions is to be considered.

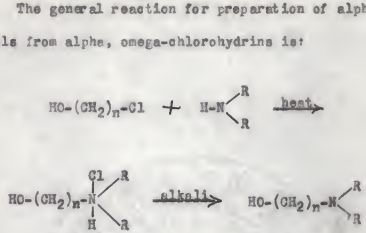
In retrospect, it is seen in this section of the dissertation that morpholinoalcohols may be satisfactorily prepared by catalytic alkylation of morpholine with glycols. Preparation of larger batches of material should result in higher yields of pure products, as there would be less loss in intermediate fractions upon distillation. Efficient fractionating columns are necessary for good yields. Indications are that the aminoalcohol and diamine are obtained in essentially equal yields, so probably not over a 50%

yield of aminoalcohol may be obtained by the alkylation method.

It is concluded that more experimentation should be done to determine the best conditions for synthesis of aminoalcohols by alkylation of amines with glycols. Not enough experimental facts have been obtained for the formulation of theories of the alkylation reaction.

The Chlorohydrin Method

The general reaction for preparation of alpha, omega-aminoalcohols from alpha, omega-chlorohydrins is:

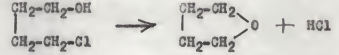


where the R's are alkyl groups. The procedure generally used is to isolate the intermediate hydrochloride and then react it with alkali.[6] However, if two moles of amine and a solvent are used, a solid amine hydrochloride is formed, and may be filtered off from the aminoalcohol simultaneously formed.[29]

After some experimentation, a regular procedure was adopted for the present research. Two moles of amine were used for each mole of chlorohydrin. The main purpose of this procedure was to insure complete reaction. It was found that heating for five hours on the water bath was sufficient. The product was then treated with potassium carbonate, and the aminoalcohol appropriately purified. Sample procedures are given at the end of this section.

The chlorohydrin method was found to give almost quantitative crude yields in every case except when tetramethylene and pentamethylene chlorohydrins were used. In these cases, side reactions reduced

yields. In the preparation of 4-morpholinobutanol-1, for example, a crude yield of 72% was obtained. Tetramethylene oxide was identified among the reaction products by boiling point and odor. Evidently the following side reaction took place:



In the 5-morpholinopentanol-1 preparation, no oxide was identified. A crude yield of 64% was obtained. The low yield could be accounted for in part at least by a poor ether extraction, as the aminoalcohol is appreciably soluble in water. Evidence to support this is found in the preparation of N-phenyl,N'-(5-hydroxypentyl) piperazine. A crude yield of 85% was obtained.

All of the aminoalcohols herein reported except 7-morpholinoheptanol-1 were made by this method. The physical and analytical data for the morpholinoalcohols is recorded in Tables I and II; for the N-phenylpiperazine series, in Table VII. Tables V and VI contain data on the dimorpholinoalkanes obtained as by-products in the preparation of morpholinoalcohols by catalytic alkylation of morpholine.

SAMPLE PROCEDURES

Preparation of 8-Morpholinooctanol-1

0.15 mole (25 g.) of Cl-$(CH_2)_8$-OH and 0.30 mole (26.5 g.) morpholine were refluxed gently for 5 hours. The product solidified on cooling. 40 cc. of 5 M K_2CO_3 (0.20 mole) was added and all was heated. A brown liquid layer separated on top and was separated with a separatory funnel. Enough H_2O was added to the lower layer to dissolve all salts. It was then extracted three times with ether, and the extracts were added to the previously separated layer. The liquid was then dried a while over solid K_2CO_3, poured off, and distilled through column G at 5 mm. after the ether was distilled off. After a small first fraction of 3 g., one main fraction, B. P. 163-163.2° (uncorr), weight 29.1 g., was collected. The yield was 90%. $N_D^{26.5}$ 1.4738

Preparation of N-β,N'-(5-Hydroxypentyl) Piperazine

0.20 mole (24.5 g.) Cl-$(CH_2)_5$-OH was heated 5 hours on the water bath with 0.40 mole (64.8 g.) of N-β-piperazine. The product was a reddish-brown solid on cooling. 42 cc. of 5 M K_2CO_3 (0.21 mole K_2CO_3) was added and heating resumed, with shaking. A dark brown liquid separated out above the carbonate layer. This solidified on cooling, and was separated and washed with water. It was then recrystallized from 300 cc. of ethyl alcohol. White crystals, melting 73-5°, were obtained. These were dried overnight in a vacuum desiccator over fused KOH. Wt. 42.2 g. (85% of the theoretical). The material was recrystallized from ligroin (B. P. 70-100°). M. P. 74.5-76.5°. Recrystallized again, M. P. 75.7-76.3°. Dried in vacuum desiccator (over KOH) to a constant weight. Weight, 33 g..

Purification of Compounds

The morpholinealcohols were all purified by vacuum distillation. The N-ø,N'-(omega-hydroxyalkyl) piperazines were all purified by first recrystallizing from 50% alcohol and drying, and finally recrystallizing from ligroin (B. P. 70-100°) repeatedly until the melting point range was 1.5° or less. Generally two or three recrystallizations were sufficient.

Preparation of Derivatives

Derivatives first chosen for the morpholinealcohols were the alpha-naphthyl urethanes. However, several of these could be obtained only as oils, so the phenyl urethanes were made in these cases.

In the N-ø,N'-(omega-hydroxyalkyl) piperazine series, all of the derivatives made were phenyl urethanes.

Data on derivatives is recorded in Tables III and VIII.

Characterization of Compounds

Nitrogen analyses were run on all thirty-five new compounds prepared. Neutral equivalents were obtained for the fourteen new aminoalcohols and the seven new diamines using methyl orange indicator with a color standard buffered to a pH of four. Densities and refractive indices of the eight liquids obtained were taken. The molecular refractions were calculated and checked with the sums of the atomic refractions.

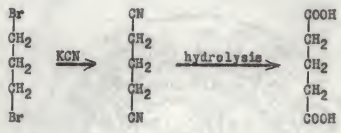
SAMPLE DERIVATIVE PREPARATION

Preparation of N-ϕ,N'-(10-Hydroxydecyl) Piperazine

0.02 mole (6.4 g.) of the aminoalcohol was dissolved in hot ligroin (B. P. 70-100°) and 0.02 mole (2.4 g.) of phenyl isocyanate dissolved in ligroin was added. The solution was heated awhile, then filtered and allowed to cool. White crystals separated. These were filtered off and recrystallized from ligroin. The M. P. was then between 91-95°. A second recrystallization gave a M. P. 95-96°. The compound was dried to constant weight and bottled.

Preparation of Intermediates

The alpha, omega-dibasic acids required for this investigation were succinic, glutaric, adipic, pimelic, suberic, azelaic, and sebacic. Of these, succinic, adipic and sebacic were purchased. Glutaric acid was prepared from trimethylene bromide[30]:



Pimelic acid was the most difficult to prepare in quantity. It was synthesized in the usual way from salicylic acid[31]. Mr. L. J. Kitchen also prepared some for the author by a malonic ester synthesis from trimethylene bromide.

Suberic and azelaic acids were obtained by nitric acid oxidation of ricinoleic acid, following the procedure of Baker and Ingold[32].

The butyl esters of all seven acids were made by refluxing with butanol under a column with a special esterification head. This was designed by Mr. J. P. Bain of this laboratory for the purpose of removing water as it is formed. It was similar to a column reported by Doran[33]. With use of this equipment, the yields of ester were almost quantitative. Boiling points of the esters are recorded in Table IX.

Alpha, omega-glycols were obtained from the butyl esters by catalytic hydrogenation at high pressures and temperature, using the method of Adkins and co-workers [22,23,24,25]. About 30 grams of copper-chromium oxide catalyst per mole of ester was used. Hydrogen pressure was maintained at 2,000 - 6,000 pounds per square inch, and the temperature was kept between 240-270° during the reduction. The time of reduction varied from two to eight hours, depending mainly upon the quality of catalyst used. Shaking of the bomb was continued until the gauge indicated that hydrogen absorption had stopped. Upon cooling, the bomb was opened and the catalyst filtered off, preferably with a filter aid such as Johns-Manville's "Hyflow Supercel". The butanol was distilled off at atmospheric pressure, or with the use of an aspirator. Finally, the remaining product was fractionated through a column at reduced pressure. Yields of pure material were generally about 80%. Data on the glycols is recorded in Table X. They have all been prepared previously, and are fully reported in the literature.

Alpha, omega-chlorohydrins, of general formula $Cl-(CH_2)_n-OH$, were prepared directly from the glycols. Where n was 4 and 5, Darzen's reaction was used, following the procedure of Kirner and Richter.[34] Thionyl chloride is the reagent:

$$HO-(CH_2)_n-OH + SOCl_2 \longrightarrow Cl-(CH_2)_n-OH + SO_2 + HCl$$

Satisfactory yields of 35 and 33% respectively were obtained. Where n was 6,7,8,9, and 10, the method of Bennett and Moses[35] was found

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to be best. The glycol was heated to 70° in the presence of a large excess of concentrated hydrochloric acid, and was continuously extracted with heptene (B. P. 95-100°). At this temperature, 50 hours extraction gave yields of around 65% of pure chlorohydrin, agreeing with yields obtained by Bennett and Moses. The literature has few references to alpha, omega-chlorohydrins. The physical data obtained in this investigation indicate that the chlorohydrins were purer than those obtained by Bennett and Moses. Probably better fractionating columns were used here. Data obtained here is recorded in Table XI and Figure II; data found in literature is in Table XII.

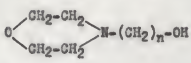
In this investigation, derivatives of four chlorohydrins were made for comparison with those in the literature. Melting points of the alpha-naphthyl urethane of pentamethylene chlorohydrin, the phenyl urethane of octamethylene chlorohydrin, and the alpha-naphthyl urethane of tetramethylene chlorohydrin agree with values recorded in the literature. The phenyl urethane of nonamethylene chlorohydrin melted 3° higher than recorded in literature. Also prepared was the phenyl urethane of decamethylene chlorohydrin. It has not been reported previously.

Experimental data on the chlorohydrin derivatives is recorded in Table XIII.

Table I (see Figure I)

MORPHOLINOALCOHOLS

General Formula:



PHYSICAL DATA

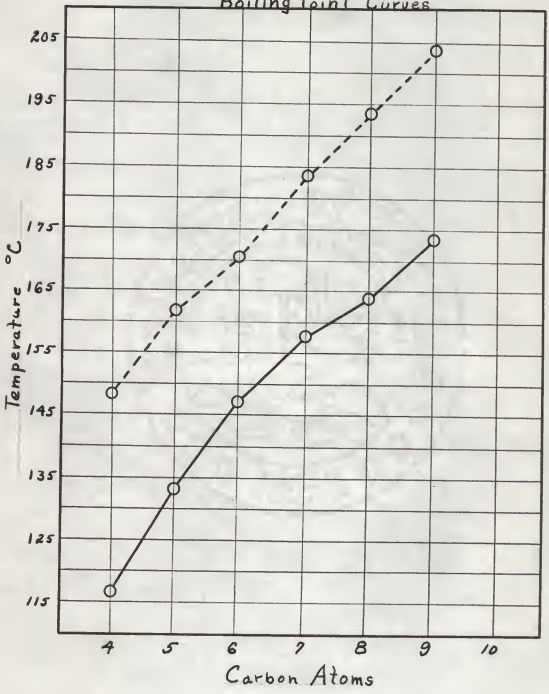
n	Boiling Point °C (corr.)	mm. pressure	Melting Point °C (corr.)	Refractive Index	Density D_4^{25}
4	116.5-7.0	5	---	N_D^{24} 1.4745	1.018
5	133.0-3.5	5	---	N_D^{24} 1.4755	1.005
6	146.0-7.0	5	---	N_D^{25} 1.4750	0.9884
7[a]	155.5-8.0	5	---	N_D^{25} 1.4747	0.9783
8	164.0-4.2	5	---	$N_D^{26.5}$ 1.4737	0.9675
9	173.0-3.5	5	31	$N_D^{26.5}$ 1.4735[b]	-------
10	164.0-5.0	2	39.5-40.5	N -------	-------

a --- Prepared by alkylation of morpholine with heptamethylene glycol only.

b --- Taken right after distillation before solidification.

Figure I

Boiling Point Curves



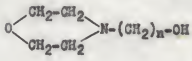
---- Dimorpholinoalkanes —— Morpholinoalcohols

Pressure 5 mm.

Table II

MORPHOLINOALCOHOLS

General Formula:



ANALYTICAL DATA

n	Molecular Weight	Neutral Equivalent (Methyl orange)	Molecular Refractions: Lorenz-Lorentz eq.	Molecular Refractions: Sum of atomic refractions	Analyses, %N: Calc.	Analyses, %N: Found
4	159.2	159.3	43.93	44.05	8.81	8.92
5	173.2	173.2	48.50	48.67	8.09	8.09
6	187.3	184.9	53.30	53.29	7.49	7.34
7	201.3	203.6	57.80	57.91	6.96	6.93
8	215.3	214.7	62.55	62.52	6.51	6.37
9	229.3	227.6	---	---	6.11	5.86
10	243.3	243.5	---	---	5.76	5.66

Neutral equivalents calculated from: $\frac{\text{Wt. sample} \times 1000}{\text{Ml. acid} \times \text{Normality of acid}}$

Molecular refractions calculated from: $\frac{\text{Molecular wt.}}{\text{density}} \times \frac{n^2-1}{n^2+2}$ (Lorenz-Lorentz equation)

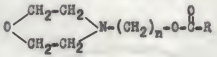
Atomic refractions taken from Gilman, Organic Chemistry, Vol. II, p. 1739 (John Wiley, 1938)

Table III

ARYL URETHANES OF

MORPHOLINOALCOHOLS

General Formula:



Where R is either phenyl: or α-naphthyl:

n	R	Melting Point °C (corr.)	Analyses, %N Calc.	Found
4	Phenyl	86.0-87.0	10.07	9.80
5	Phenyl	55.5-57.0	9.58	9.32
6	α-Naphthyl	71.0-72.0	7.86	7.53
7	Phenyl	71.0-72.0	8.74	8.56
8	α-Naphthyl	73.0-74.0	7.29	6.96
9	α-Naphthyl	54.0-56.0	7.03	6.83
10	α-Naphthyl	66.5-67.5	6.79	6.75

All urethanes were recrystallized from ligroin (B. P. 70-100°).

Table IV

MORPHOLINOALCOHOLS BY ALKYLATION

Glycol	Moles used	Moles of Morpholine	cc. Dioxane (solvent)	Yields of Pure Compound, % Alcohol	Diamine	grams Cu-CrO cat. used
Tetramethylene	0.75	0.94	250	36	22	22
Pentamethylene	0.80	1.0	300	31	28	24
Hexamethylene	0.60	0.60	300	21	18	20
Heptamethylene	0.33	0.42	125	19	28	10
Octamethylene	0.50	0.75	300	26	41	15
Nonamethylene	0.34	0.43	250	38	28	11
Decamethylene	0.40	0.40	300	21	13	9

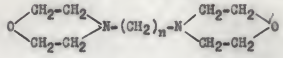
In every case, the bomb was shaked for 6 hours at 235-270°C.

Yields are based on the glycol used. Some of the glycol did not react in each case, but was not recovered pure, so yields were not adjusted for it.

Table V (see Figure I)

α,ω -DIMORPHOLINOALKANES

General Formula:



PHYSICAL DATA

n	Boiling Point °C (corr.)	mm. pressure	Melting Point °C (corr.)	Refractive Index		Density D_4^{25}
4	147.5-8.5	5	51.5-52.5	$N_D^{25.5}$	1.4825	--------
5	161.0-2.0	5	liquid	N_D^{25}	1.4804	0.9980
6	169.5-171	5	35.5-38.5	N_D^{25}	1.4815	--------
7	183.0-4.0	5	liquid	$N_D^{26.7}$	1.4797	0.9789
8	191.5-3.5	5	46.5-47.5[a] 48	----------		--------
9	203.5-4.0	5	liquid	$N_D^{24.7}$	1.4790	0.9639
10	187.0-9.0	2	48.0-49.0[b] 50.5-51.5	----------		--------

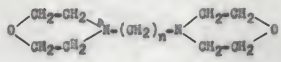
a --- Double melting point after recrystallization from ethyl alcohol. Not as sharp as 10- below.

b --- Double melting point, after several recrystallization from 50% alcohol. (Original material melted 45-49°). After the first melting, definite crystals formed, but all did not solidify before remelting. The compound had been dried 10 days in a vacuum desiccator over fused KOH.

Table VI

α,ω -DIMORPHOLINOALKANES

General Formula:



ANALYTICAL DATA

n	Molecular Weight	Neutral Equivalent (Methyl orange)	Molecular Refractions: Lorenz-Lorentz eq.	Molecular Refractions: Sum of atomic refractions	Analyses, %N: Calc.	Found
4	228.2	114.7	---	---	12.28	12.00
5	242.3	121.3	69.29	69.10	11.56	11.32
6	256.3	129.3	---	---	10.93	10.76
7	270.4	136.3	78.46	78.34	10.37	10.18
8	284.4	141.6	---	---	9.85	9.72
9	298.5	146.7	87.42	87.58	9.39	9.11
10	312.5	152.5	---	---	8.97	8.87

Neutral equivalents calculated from: $\frac{\text{Wt. sample} \times 1000}{\text{Ml. acid} \times \text{Normality of acid}}$

Molecular refractions calculated from: $\frac{\text{Molecular wt.}}{\text{density}} \times \frac{n^2-1}{n^2+2}$ (Lorenz-Lorentz equation)

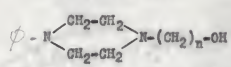
Atomic refractions taken from Gilman, Organic Chemistry, Vol. II, p. 1739 (John Wiley, 1938)

Table VII (see Figure III)

N-PHENYL,N'-(ω-HYDROXYALKYL)

PIPERAZINES

General Formula:



PHYSICAL AND ANALYTICAL DATA

n	Molecular Weight	Neutral Equivalent (methyl orange)	Melting Point °C (corr.)	Analyses, %N Calc.	Found
4	234.3	236.0	59.0-60.0	11.96	11.81
5	248.4	248.3	74.0-75.0	11.28	11.13
6	262.4	262.7	65.5-67.0	10.68	10.52
7	276.4	274.9	75.5-76.5	10.14	10.06
8	290.4	294.4	57.0-58.5	9.65	9.43
9	304.5	303.1	80.0-80.5	9.20	9.14
10	318.5	317.1	67.0-68.0	8.80	8.74

All were white, crystalline compounds.

All were recrystallized first from 50% alcohol, dried thoroughly, and recrystallized again from ligroin (B. P. 70-100°) until pure.

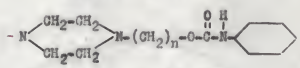
Table VIII (see Figure III)

PHENYL URETHANES OF

N-PHENYL,N'-(ω-HYDROXYALKYL)

PIPERAZINES

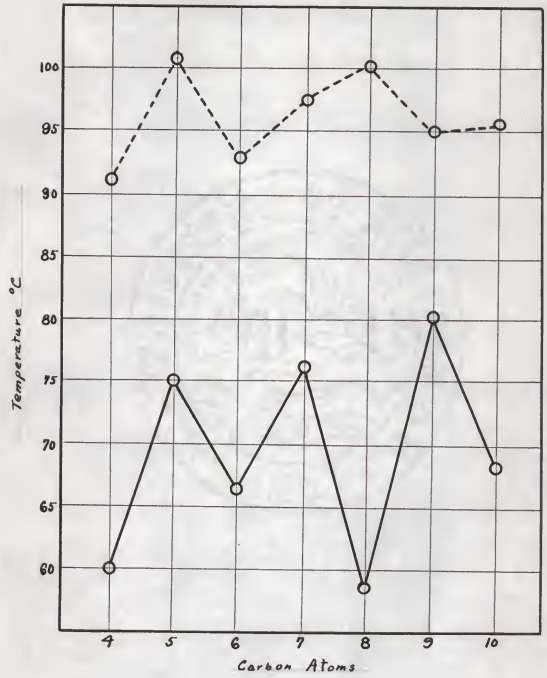
General Formula:



n	Molecular Weight	Melting Point °C (corr.)	Analyses, %N Calc.	Found
4	353.4	91.0-92.2	11.98	11.64
5	367.4	100.1-101.5	11.44	11.24
6	381.5	91.5-93.0	11.01	10.91
7	395.5	96.5-97.5	10.63	10.46
8	409.6	99.5-100.5	10.26	10.09
9	423.6	94.0-95.0	9.92	9.78
10	437.6	95.0-96.0	9.60	9.45

All the phenyl urethanes were white crystalline compounds. They were best prepared by dissolving the alcohol in hot ligroin (B. P. 70-100°), adding an equimolecular quantity of phenyl isocyanate in ligroin, and heating a while. The solution was filtered hot. The urethane crystallized on cooling. Two recrystallizations thereafter were generally sufficient.

Figure III



Melting Points

---- Ø-Urethanes of N-Ø,N'-(ω-hydroxy alkyl) Piperazines

—— N-Ø,N'-(ω-hydroxyalkyl) Piperazines

Table IX

DI-(n-BUTYL) ESTERS OF α,ω-ACIDS

General Formula:

$C_4H_9OOC-(CH_2)_n-COOC_4H_9$

n	Name of Acid	Boiling Point of Ester	Pressure, mm. Hg.
4	succinic	112.5	2.0
5	glutaric	134-5 129.5-30.5	4.5 3.3
6	adipic	117 154-6	0.5 7.0
7	pimelic	177-8 (corr.)	10.0
8	suberic	158-61	3.5
9	azelaic	173.5-5.5 (corr.)	3.5
10	sebacic	178.5-9.5	3.0

Table X

α,ω-GLYCOLS

General Formula:

$HO-(CH_2)_n-OH$

n	Boiling Point	Pressure, mm.	Melting Point
4	120.5-2.0	10	liquid
5	129.0-30	10	-14 to -13
6	135.0-6.0 (corr.) 116.5	8 3	40
7	128.0-9.0 (corr.)	3.5	liquid
8	132.5-4.5 (corr.)	3.5	58.5-60.5 (corr.)
9	143.0-3.5	3.5	45.5-46.5 (corr.)
10	153.0-4.0	3	71-72.5 (corr.)

This data was determined in this investigation.

Table XI (see Table XII and Figure II)

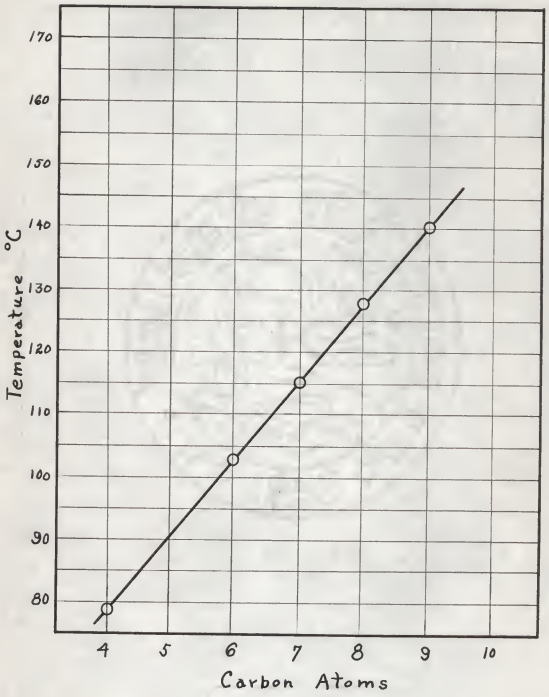
α,ω -CHLOROHYDRINS, THIS INVESTIGATION

General Formula:

$Cl-(CH_2)_n-OH$

n	Boiling Point	Pressure, mm.	Refractive Index	Yield, % (pure)
4	74-8	10	n_D^{20} 1.4517	34.8
5	77-9 (corr.)	5	n_D^{28} 1.4511	33
6	102-3 (corr.)	10	n_D^{20} 1.4555	
7	115.5 (corr.)	10	$n_D^{26.5}$ 1.4540	57
8	127-128 (corr.)	10	$n_D^{24.3}$ 1.4563	65
9	140-140.5 (corr.)	10	M. P. 28°	62.5%
10	132-3 (corr.)	4	n_D^{20} 1.4606	

Figure II



B.P. α, ω-Chlorohydrins at 10 mm.

Table XII (see Table XI)

α,ω - CHLOROHYDRINS, REPORTED IN LITERATURE

General Formula:

$Cl-(CH_2)_n-OH$

n	Boiling Point	Pressure, mm.	Refractive Index	Investigator
4	81-2	14		Starr and Hixon[36]
	85-6	16	n_D^{20} 1.4518	Kirner and Richter[34]
5[a]				Bennett and Heathcoat[37]
6	112	17		Bennett and Turner[38]
7	120	13.5		Altman[39]
	150	20	n_D^{25} 1.45367	Bennett and Moses[35]
8	139	18.5		Altman[39]
	125-40	18		Bennett and Moses[35]
9	146.5	14		Altman[39]
	140-45	20	M. P. 28	Bennett and Moses[35]
10	164-5	20		Alberti and Smieciuszewski[40]
			n_D^{25} 1.45796 M. P. 10-11	Bennett and Moses[35]

[a] No physical data reported. Urethanes prepared.

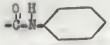
Table XIII

URETHANES OF α,ω-CHLOROHYDRINS

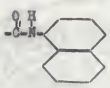
General Formula:

$$Cl-(CH_2)_n-O-R$$

Where R is:



(phenyl urethane)

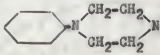


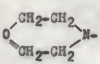
(α-naphthyl urethane)

n	R	M. P., °C Found	M. P., °C Literature
4	α-naphthyl	68.0-69.5	69[36] ; 66[37]
5	α-naphthyl	71.0-72.0	72[37]
6	---	---	---
7	phenyl	---	76-7[39] ; 76[35]
8	phenyl	76.5-77.0	77[39,35]
9	phenyl	70.0-70.5	67[39,35]
10	α-naphthyl	63.0-64.0	---
	phenyl	---	72[35]

Summary

Two new series of alpha, omega-aminoalcohols have been synthesized. Physical and analytical data of these, and of their phenyl or alpha-naphthyl urethanes, are reported.

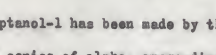
The N-phenyl,N'-(omega-hydroxyalkyl) piperazine series of general formula  , where n is 4 through 10, has been prepared from N-phenylpiperazine and chlorohydrins of the formula $Cl-(CH_2)_n-OH$.

The alpha, omega-morpholinoalcohol series of general formula  , where n is 4 through 10, has been prepared by two methods:

(1) from morpholine and alpha, omega-chlorohydrins, and

(2) by the catalyzed alkylation of morpholine by alpha, omega-glycols.

7-Morpholinoheptanol-1 has been made by the latter method only.

A series of alpha, omega-dimorpholinoalkanes, of general formula  , where n is 4 through 10, has been obtained as the other product of the catalyzed reaction of morpholine and glycols. Yields were approximately equal to the yields of aminoalcohols obtained. Physical and analytical data for this series are also reported.

From the glycols, higher over-all yields of 4-morpholinobutanol-1 and 5-morpholinopentanol-1 have been obtained by direct catalytic reaction with morpholine than through the intermediate chlorohydrins, but with higher homologs the reverse is true. More work should be done upon the catalytic alkylation method, but indications are that the maximum yields of aminoalcohols obtainable by this method cannot exceed 50%. For alpha, omega-chlorohydrins of six-carbon chains or longer, over-all yields of 55 to60% are easily obtainable. The catalytic alkylation method has the advantage of being one step shorter than the chlorohydrin method.

Alpha, omega-chlorohydrins of formula $Cl-(CH_2)_n-OH$, where n is 4 through 10, have been satisfactorily prepared by methods reported in the literature. In several instances, purer compounds than hitherto reported have been obtained.

Bibliography

1. Hartung, Walter H., Epinephrine and Related Compounds: Influence of Structure on Physiological Activity, Chem. Rev. 9, 389 (1931)
2. V. Braun and Deutsch, Ber. 45, 2504 (1912)
3. Rohmann and Schlurle, Chemical Constitution and Local Anesthetic Action in Alkamine Esters of p-Hydroxybenzoic Ethers, Arch. Pharm. 274, 110-26 (1936)
4. Magidson and Strukov, Arch. Pharm. 271, 569-80 (1933)
5. V. Braun, Ber. 49, 966 (1916)
6. British Patent 402,159, Nov. 30, 1933, to Boot's Pure Drug Co. Ltd., Frank L. Pyman and Hyman H. L. Levene
7. Adkins, Kuick, Farlow, and Wojcik, Jour. Am. Chem. Soc. 56, 2425 (1934)
8. Paden and Adkins, Jour. Am. Chem. Soc. 58, 2487-99 (1936)
9. Sauer and Adkins, Jour. Am. Chem. Soc. 60, 402-6 (1938)
10. Hill and Adkins, Jour. Am. Chem. Soc. 60, 1033 (1938)
11. Wilson, A. L., New Aliphatic Amines, Ind. Eng. Chem. 27, 867-71 (1935)
12. Gardner and Haenni, Some New Local Anesthetics Containing the Morpholine Ring, Jour. Am. Chem. Soc. 53, 2763-9 (1931)
    55, 2999 (1933)
    58, 1360-1 (1936)
13. Leffler and Brill, Alkamine Esters: Procaine Analogs III, Jour.

Chem. Soc. 55, 365-70 (1933)

14. Prelog and Driza, Coll. Czechoslovak Chem. Comm., 5, 497-502 (1933)

15. Pollard and MacDowell, Jour. Am. Chem. Soc. 56, 2199 (1934)

16. Adelson and Pollard, Jour. Am. Chem. Soc. 57, 1430 (1935)

17. Prelog and Blazek, Coll. Czechoslovak Chem. Comm. 6, 549 (1934)

18. Rider, Jour. Am. Chem. Soc. 52, 2115-8 (1930)
58, 1079-81 (1936)

19. Rider, U. S. Patent 2,004,132

20. Adkins, Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts, 97-99, The University of Wisconsin Press, (1937)

21. Ibid., 113, 118, 119

22. Ibid., 97-104

23. Folkers and Adkins, Jour. Am. Chem. Soc. 53, 1095 (1931)
54, 1145-54 (1932)

24. Wojcik and Adkins, Jour. Am. Chem. Soc. 55, 4939 (1933)

25. Adkins, Wojcik, and Covert, Jour. Am. Chem. Soc. 55, 1669-76 (1933)

26. See reference 20, page 13; Connor and Adkins, Jour. Am. Chem. Soc. 54, 1138, (1932)

27. Paden and Adkins, Jour. Am. Chem. Soc. 58, 2487 (1936)

28. Hill and Adkins, Jour. Am. Chem. Soc. 60, 1033 (1938)

29. Basilerados, Condensation of Chlorohydrins with Piperidine, Bull. soc. chim. (5), 4, 1131-6 (1937)

30. Organic Synthese, 10, 58, John Wiley and Sons, (1930)

31. Organic Synthese, 11, 43, John Wiley and Sons, (1931)

32. Baker and Ingold, Jour. Chem. Soc. CXXIII, 128 (1923)

33. Doran, Ind. Eng. Chem. , Anal. Ed., 5, 101 (1933)

34. Kirner and Richter, Jour. Am. Chem. Soc. 51, 2503 (1929)

35. Bennett and Moses, Jour. Chem. Soc. 1931, 1697 (1931)

36. Starr and Hixon, Org. Syn. 17, 84 (1937)
Jour. Am. Chem. Soc. 56, 1595 (1934)

37. Bennett and Heathcoat, Jour. Chem. Soc. 1929, 268 (1929)

38. Bennett and Turner, Jour. Chem. Soc. 1938, 813-15 (1938)

39. Altman, Rec. trav. chim. 57, 941-63 (1938)

40. Alberti and Smieciuszewski, Monats. fur Chemie. 27, 412

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Biography

George Washington Anderson was born October 7, 1913 at Gainesville, Florida. He received his pre-collegiate training in the public schools of Gainesville, and was graduated from the University of Florida in 1935 with the Degree of Bachelor of Science with High Honors. He has attended the University of Florida continuously from 1931 to the present time.

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Committee Report

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee and has been approved by all members of the Committee. It was submitted to the Graduate Council and was approved as partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Date May 29, 1939

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